REMARKS

I. Status of the Claims

Claims 19-36 and 38-39 are pending in the application. Claims 19-29, 32, and 34-36 have been withdrawn from consideration as being drawn to non-elected subject matter. Claims 30, 31, 33, and 37-39 have been rejected. Claim 37 has been canceled rendering rejections of this claim moot.

Applicants have amended the claims 30, 33, 38, and 39 solely to more clearly describe that which they consider to be their invention. The amendment of claim 30 adds a recitation of "binding to" to further clarify the criteria for determining whether a test compound inhibits a HCV polymerase. Support for this amendment is found in the specification, for example, at page 12, lines 7-22. Claims 30 and 33 have been amended to recite only the polypetides related to $NS5B_{570}$, and/or $NS5B_{544}$, $NS5B_{536}$, and $NS5B_{531}$. Support for all amendments is found in the application as filed. No new matter has been added.

II. Priority

The Office acknowledges Applicants' claim for foreign priority under 35 U.S.C. § 119 (a)-(d). Office Action, page 2. The Office then mischaracterizes the Applicants' benefit of priority by concluding "the instant application does not receive the priority benefit of [the two] foreign applications...." Id.

Applicants point out that under the provisions of 35 U.S.C. § 119, the instant application does receive the benefit of priority for all subject matter in common between the instant application and the two priority applications JP 11-188630, filed July 2, 1999

("JP'630"), and JP 11-192488, filed July 7, 1999 ("JP'488"). The priority applications do disclose subject matter in common with the instant application.

III. Indefiniteness Rejection

Claims 30, 31, 37, and 38 have been rejected as allegedly indefinite under 35 U.S.C. § 112, second paragraph. *Id.*, pages 2-3.

The Office alleges that claim 30 is indefinite for reciting "complementary" at lines 14-15 *Id.*, page 3. Applicants have amended the claim to make more clear that "binding" criteria may be used to determine whether a test compound inhibits HCV polymerase.

Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Enablement Rejection

The Office has maintained the rejection of claims 30, 31, 33, and 37-39 under 35 U.S.C. § 112, first paragraph, asserting that the specification, while being enabling for a crystal structure of HCV polymerase using $NS5B_{570, 544, 536}$ and $_{531}$, does not reasonably provide enablement for all HCV polymerase." Office Action, page 3. Applicants traverse the rejection for reasons of record.

In order to advance prosecution, however, Applicants have amended the claims to recite HCV polymerase polypeptides comprising sequences corresponding to $NS5B_{570, 544, 536}$ and $_{531}$. Applicants submit that the specification fully enables the claims as amended. Applicants reserve the right to seek patent protection on the subject matter of the original claims in a continuing application.

Applicants therefore respectfully request reconsideration and withdrawal of the

rejection.

V. Obviousness Rejections

Claims 30, 31, 33, and 37-39 are rejected under 35 U.S.C. § 103(a) as being obvious over Kim *et al.*, U.S. Patent 6,183,121 ("'Kim") in view of *In re Gulack*, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983) taken with Bressanelli *et al.* Proc. Natl. Acad. Sci. USA 96:13034-13039 (1999) ("Bressanelli"); and over Kim in view of *In re Gulack*. Office Action, pages 9-12. In view of the amendment canceling claim 37, the rejection of that claim is moot. Applicants traverse these rejections for reasons of record and as supplemented below.

Kim in view of Bressanelli

Kim and Bressanelli Do Not Teach All Recited Limitations of Claims 38 and 39

In order to render a claim obvious under 35 U.S.C. § 103(a), the cited references must teach or suggest all of the recited limitations of the claim. In this instance, the Office admits that Kim does not teach or suggest the three-dimensional structural coordinates of a NS5B HCV polymerase. Office Action, page 8. Bressanelli discloses a single NS5B HCV polymerase having only the 531 amino-terminal residues. Page 13034. Claims 38 and 39 as amended do not recite an NS5B polypeptide NS5B HCV polymerase having an amino acid sequence X-Y, wherein X is a consecutive amino acid sequence which is a portion of NS5B, the N-terminal amino acid of X is a serine residue corresponding to amino acid residue 1 of NS5B, and the C-terminal amino acid residue of X is amino acid residue 531. Applicants submit that nothing in the combination of

references suggest any of the other specifically recited continuous NS5B polypeptide residues. Accordingly, the combination of references do not teach or suggest all of the recited limitations of claims 38 and 39. Applicants respectfully request reconsideration and withdrawl of the rejection of these claims.

No Motivation to Combine the References

The suggestion to combine or modify the prior art teachings must be clear and particular. *See In re Dembiczak,* 175 F.3d 994, 999 (Fed. Cir. 1999). Thus, while a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the prior art, that modification is not obvious unless the prior art suggested the desirability of such a modification. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984). Furthermore, the Office has the burden to provide some objective evidence, not found in the Applicants' specification, or reasoned argument showing that one of ordinary skill in the art would have been motivated to combine the prior art to devise the claimed invention. *In re Lee*, 277 F.3d 1338, 1433 (Fed. Cir. 2002).

Applicants submit that the Office has failed to establish a *prima facie* case of obviousness because there simply is no clear and particular suggestion in the cited references to combine the crystal structure of HCV polymerase polypeptide $NS5B_{531}$ of Bressanelli with Kim's method of using HCV helicase crystal structure for identifying helicase inhibitors to devise the claimed invention.

Kim discloses that "[p]roteolytic processing of the HCV polyprotein by virally encoded proteases generates several nonstructural (NS) proteins with enzymatic activities essential for the replicative cycle of the virus." Col. 1, lines 47-49. Each of

these NS proteins perform very different functions. For example, "NS2 encodes a presumed metalloprotease, NS5B is a RNA-dependent RNA polymerase, and NS3 is a bifunctional enzyme..." Col. 1, lines 51-55. NS3 is a serine protease and a helicase, performing "an intramolecular cleavage at the NS3/NS4A junction to form a tight noncovalent NS3-NS4A complex necessary for efficient pressing of the remaining polyprotein." Col. 1, lines 53-59. Kim relies on an HCV helicase complexed 1:1 with an oligonucleotide of 8 uracil nucleotides (dU_8) in order to obtain a three dimensional crystal structure of helicase binding pockets. Col. 5, line 35, to col. 6, line 8. Kim discloses that 3 binding pockets are found for their HCV helicase-dU_8 complex, designated U4-, U8-, and NTP-like. Col 6, lines 5-44. Kim then defines a shape for each pocket by designating the specific amino acids associated with each pocket. Col. 6, line 55, to col. 7, line 33.

Bressanelli discloses a crystal structure of an HCV polypeptide corresponding to the 531 amino-terminal residues of NS5B. Page 13034, second column. "as a key step to developing specific anti-HCV drugs that interfere with viral replication, we have crystallized this catalytic fragment." Id.

The Office concludes

> an artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the concept emphasized by Kim et al. for a method that uses molecular design techniques to identify, select and design chemical entities, including inhibitory compounds based on the 3-dimensional structure of a polymerase and apply such method to the crystal structure for RNA-dependent RNA polymerase of hepatitis C virus as disclosed by Bressanelli et al.

Office Action, page 9. Applicants disagree.

Applicants note that the Office has incorrectly characterized Kim's target peptide, HCV helicase, as a "polymerase", when only serine protease and helicase functions are indicated. Col. 1, lines 53-59. The Office appears to be suggesting that Kim's method that uses molecular design techniques to identify, select and design chemical entities specific for HCV helicase based on the 3-dimensional structure of a helicase-oligonucletide complex can be used to devise a method to select and design chemical entities specific for HCV NS5B polymerase based on the 3-dimensional structure of Bressanelli's HCV NS5B polymerase. Applicants, however, submit that such a suggestion is not apparent in the combination of references.

While Bressanelli indicates that their NS5B crystal structure is "a key step to developing specific anti-HCV drugs" they provide no further indication of any other steps required to further develop such specific drugs. Applicants submit that Kim's method provides no suggestion that it could be applied to crystal structures for other HCV polymerase. Kim's resolution of their helicase binding pockets required that the helicase be complexed with a target nucleotide (pU_8). Applicants submit that one of skill in the art reading the combination of references would not conclude that Bressanelli's HCV polypeptide crystal structure could be readily applied to Kim's method because Kim's method requires the HCV polypeptide to be complexed with a helicase target molecule and Bressanelli's crystal structure was not obtained as a complex with a polymerase target molecule.

In view of the above, Applicants contend that the Office has, through prohibited hindsight, selected a combination that might be feasible, but has not proffered clear and particular evidence concerning the desirability of combining Kim's helicase-target

complex crystal structure approach with Bressanelli's target-free polymerase crystal structure to devise the instant invention. Moreover, "a general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995). At best, it may have been obvious to try such a combination. However, obvious to try is not the standard. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); M.P.E.P. § 2145(X)(B). The only motivation to combine the references and derive the claimed invention comes from the Applicants' own specification.

For this reason as well, Applicants respectfully request that the Office reconsider and withdraw the rejection.

Erroneous Application of *In re Gulack*

The Office alleges that "...the specific limitations of three-dimensional structural coordinate[s] drived from a HCV polymerase in this instant case do not distinguish the invention from the prior art in term[s] of patentability because they are descriptive nonfunctional subject matter." Office Action, page 8. The Office thus combines the cited references with *In re Gulack*, 217 USPQ 401, 404 (Fed. Cir. 1983) and asserts that:

> *In re Gulack* defines nonfunctional descriptive material, as when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in term[s] of patentability. Also, the MPEP indicates that descriptive material that cannot exhibit any functional interrelationship with the way in which computing processes are performed does not constitute a statutory process, machine, manufacture or composition (MPEP § 2106 (IV)(B)(b)).

Office Action, page 8. Applicants disagree with the Office's characterization of the claimed subject matter as being "descriptive nonfunctional subject matter," and disagree with the Office's present application of *In re Gulack*. Applicants note that MPEP § 2106(IV)(B)(b) concerns patentable subject under 35 U.S.C. § 101, and offers no explicit guidance for rejecting claims as obvious under 35 U.S.C. § 103(a).

Applicants submit that the Office has erred in applying *In re Gulack* to the present case. *In re Gulack* addresses "printed matter" rejections. Specifically, *In re Gulack* holds that "[w]here the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability." *In re Gulack*, 217 USPQ at 404.

More recently, however, the Court further clarified its position on this issue in *In re Lowry*, 32 USPQ.2d 1031 (Fed. Cir. 1994). The *Lowry* Court rejected a previous attempt by the Office to apply the printed matter rejection in other contexts.

> The printer matter cases[, e.g., *Gulack*,] dealt with claims defining as the invention certain novel arrangements of printed lines or characters, useful and intelligible only to the human mind. The printed matter cases have no factual relevance where the invention as defined by the claims requires that the information be processed not by the mind but by a machine, the computer.

Lowry, 32 USPQ.2d at 1034 (internal quotations and citation omitted). The present claims are drawn to methods of interpreting complex three-dimensional molecular structure with structural resolutions on the order of Angstroms, not printed lines and characters. Accordingly, Applicants submit that the cited printed matter cases are not relevant to Applicants' claimed invention.

Further, while the Court in both *In re Lowry* and *In re Gulack* applied the standard for determining when a claim contains impermissible descriptive nonfunctional matter, it is important to note that in both cases the Court applied the standard to the facts in these cases and determined that the claims did not contain impermissible descriptive nonfunctional matter, and were not obvious over the prior art.

The irrelevancy of the cited cases notwithstanding, Applicants submit that, contrary to the Office's position, the claim recitations at issue are indeed "functionally descriptive subject matter." Recitation that the NS5B crystal structure is used to identify complementarity of a test compound involves resolution of whether a test compound is complementary to said active site and/or RNA binding cleft of said polypeptide and inhibits a HCV polymerase by binding to said active site and/or RNA binding cleft of said HCV polymerase. Far from being "structural coordinates...are merely stored so as to be read or outputted by a computer without creating any functional relationship," as asserted by the Examiner, determining whether a test compound is complementary to said active site and/or RNA binding cleft of said polypeptide and inhibits a HCV polymerase by binding to said active site and/or RNA binding cleft of said HCV polymerase, by definition, is performed differently from determining inhibitors of an HCV helicase binding pocket. Therefore, Applicants submit that the recitations of HCV NSB5 polypeptide crystal structures are not mere descriptive nonfunctional subject matter; they are not mere markings on paper.

Accordingly, Applicants submit that the claims as amended are allowable.

No Reasonable Expectation of Success

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success of combining the cited references to arrive at the claimed invention. M.P.E.P. § 2143.

Applicants submit that there is no indication that Kim's method for resolving HCV helicase binding pockets would be equally successful for resolving putative binding pockets for a HCV polymerase from the three-dimensional crystal structure of a polymerase peptide. For example, the structural and functional properties of Kim's HCV helicase and Bressanelli's polymerase peptide are very different and result in totally different three-dimensional structure determinations. Further, as noted above, Kim required that the helicase be complexed with a target nucleotide (pU_8) in order to resolve binding pockets. Bressanelli's crystal structure, however, was not obtained as a polymerase-target molecule complex, and therefore one reading Kim would not have a reasonable expectation that Bressanelli's crystal structure was obtained under appropriate conditions to model accessible binding pockets during HCV polymerase ligand binding. For these reasons, Applicants submit that one of ordinary skill reading the combination of references would not have a reasonable expectation of successfully combining the references to devise the claimed invention.

For any of the reasons above, Applicants respectfully request reconsideration and withdrawal of the rejection.

Kim

Kim Does Not Teach All The Recited Claim Limitations

In order to render a claim obvious under 35 U.S.C. § 103(a), the cited reference must teach or suggest all of the recited limitations of the claim. In this instance, the Office admits that Kim does not teach or suggest the three-dimensional structural coordinates of any NS5B HCV polymerase, and more specifically does not teach or suggest the coordinates for a NS5B HCV polymerase having an amino acid sequence X-Y, wherein X is a consecutive amino acid sequence which is a portion of NS5B, the N-terminal amino acid of X is a serine residue corresponding to amino acid residue 1 of NS5B, and the C-terminal amino acid residue of X is selected from amino acid residues 531, 536, 544, and 570. Office Action, page 11.

The Office, however, alleges that the three-dimensional structural coordinates of the claims "do not distinguish the invention from the prior art in term[s] of patentability because they are descriptive nonfunctional subject matter." Id. Applicant disagree for reasons of record and as supplemented herein.

As discussed above, Applicants submit that the Office has erroneously applied *In re Gulack* to the present process claims. For example, the Office indicates that *In re Gulack* "defines nonfunctional descriptive material, as when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in term[s] of patentability." Office Action, page 11. The Court, however, is very dubious of "printed matter rejections" and points out in *In re Gulack* that " [a] 'printed matter rejection' under § 103 stands on questionable legal and logical footing." *See In re Gulack*, entire footnote No. 8.

Applicants submit that the Office has erred in applying *In re Gulack* to the present case. Applicants incorporate herein by reference all of the above arguments regarding application of *In re Gulack* and *In re Lowry* to the present claims. In view of these arguments, Applicants submit that the claimed recitations of HCV NSB5 polypeptide crystal structures are to be given patentable weight; they are not mere markings on paper. Accordingly, Applicants submit that the claims as amended are allowable.

No Reasonable Expectation of Success

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success of combining the cited references to arrive at the claimed invention. M.P.E.P. § 2143.

Applicants submit that there is no indication that Kim's method for resolving HCV helicase binding pockets would be equally successful for resolving putative binding pockets for a HCV polymerase from the three-dimensional crystal structure of a polymerase peptide. Without a teaching or suggestion that Kim's HCV helicase method can be applied to the instant HCV polymerase peptides, there can be no reasonable expectation that one skilled in the art reading Kim would successfully practice the claimed process. Therefore, Applicants submit that one of ordinary skill reading Kim would not have a reasonable expectation of successfully modifying Kim to devise the claimed invention.

For the reasons above, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the amendment and remarks presented, Applicants submit that claims 30, 31, 33, and 38 and 39 are in condition for allowance and respectfully request reconsideration of the claims, withdrawal of the rejections, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: March 23, 2004

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